## REMARKS

Upon entry of this response, claims 34, 40 and 45-70 will be pending in this application. Claims 71-74 have been previously withdrawn. Support for amended claims can be found throughout the specification. For example, amended claims 34 and 40 are supported by the specification at page 29, lines 20-25; and amended claims 69 and 70 are supported by the specification at page 5, lines 2-9, page 29, lines 20-25, and the original claim 1. Claims 45, 52, 53, 60 and 63-66 have been amended to correct typographical errors and correct antecedent basis.

### I. The Invention Has Utility

Claims 34, 40 and 45-70 stand rejected under 35 U.S.C. 101 for allegedly lacking a specific and substantial utility or a well-established utility. Principally, it appears that the Office Action is alleging that the claimed invention does not have utility because the utility asserted by the Applicants is not a "substantial" or "real world" utility.

Applicants respectfully traverse the rejection of claims 34, 40 and 45-70 under 35 U.S.C. 101 for allegedly lacking utility. Presently, the claims recite a method for directly identifying a non-endogenous candidate compound as a compound that stimulates an endogenous GPCR (or an endogenous constitutively active GPCR) or reduces the activity of an active receptor state of an endogenous GPCR (or an endogenous constitutively active GPCR), where a location of expression of the GPCR in a mammalian tissue source is known, and the receptor has been correlated with at least one mammalian physiological function, and an endogenous ligand for the GPCR has not been identified.

To properly reject a claimed invention for lack of utility, the Office Action must make a *prima facie* showing that the claimed invention lacks utility. MPEP section 2107.02 IV. To establish such a *prima facie* showing, the Office Action must provide:

(A) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is neither both specific and substantial nor well-

established;

(B) Support for factual findings relied upon in reaching this conclusion; and

(C) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

The Office Action has not established a *prima facie* showing that there is no substantial utility. Instead, the Office Action merely states a conclusion that there is no substantial utility, without any support for factual findings and without evaluating all the relevant evidence of record. For example, the Office Action concludes that the claims lack substantial utility because one of ordinary skill would not be able to correlate a GPCR at a particular location in the mammal with a disease or condition, by stating:

> a method of screening a GPCR wherein expression is correlated with a "function in the brain" but has no particular correlation with a disease would not constitute a substantial utility. A stated belief that a connection exists between a GPCR and a disease, based solely on location of GPCR expression, is not sufficient information to use the claimed method to identify compounds to treat the disease; it merely defines a starting point for further research and investigation to determine if there is actually a nexus between the GPCR and the disease.

The Office Action at page 3. Notably, the Office Action arrives at the conclusion that there is no substantial utility without providing any support for factual findings. Further, the Office Action arrives at this conclusion without evaluating all the relevant evidence of record, which clearly shows that the claimed invention has substantial utility.[1] For example, of record is Dr. Stanley Watson's November 2, 2000, Declaration (Exhibit 1). Dr. Watson's Declaration at paragraph 22.a.1(a) states that:

> In my scientific opinion, the location of a GPCR, by coupling this cellular location within specific cells, circuits, and organs, strongly links that GPCR to its physiological function...

Dr. Watson's Declaration also states that other scientists and the scientific literature have

[1] MPEP section 2107.02 VII states that "the applicant does not have to provide evidence sufficient to establish that an asserted utility is true 'beyond a reasonable doubt'...Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true." (emphasis original).

asserted similar conclusions. Dr. Watson cites a paper by Browne (Browne, M.J. in Biotechnology 78:247, 24 (2000)) and a paper by Wilson et al. (British Journal of Biotechnology 125:1387, 1388 (1998)). For example, paragraph 22.a.1(b) of Dr. Watson's Declaration states:

> Wilson, S. et al in "Orphan G-protein Coupled Receptors: The Next Generation of Drug Target" British Journal of Biotechnology 125:1387, 1388 (1998) notes that "the expression pattern can determine whether a receptor is expressed in a normal or diseased tissue of interest as a therapeutic target"

Further, Dr. Watson's Declaration provides several examples from the Applicants of specific orphan GPCRs that have been correlated with a condition based upon their location in a mammal. For example, Dr. Watson's Declaration at paragraph 22.2(a) states:

> Using routine techniques and commercially available reagents, procedures and kits I have been informed and I believe that Arena determined that this receptor [called 19AJ or RUP3] is expressed specifically in the beta cells in the islets of the pancreas. Because of the strong implications of the pancreas in insulin production, an appreciation for the role of this receptor was capable of being deduced based upon its location.

The tissue expression pattern of 19AJ (also called RUP3) strongly implicated the receptor as a therapeutic target for diabetes. Using the claimed methods, Arena has been successful in identifying compounds that stimulate (agonist) 19AJ, where the compounds effectively stimulate insulin secretion in rat islets and reduce blood glucose in animals including diabetic animals. As corroboration, Figure 1 enclosed herein as Exhibit 2, shows that these compounds are effective at stimulating insulin secretion in rat islet cells. In this model, agents that induce cAMP are not expected to stimulate insulin secretion when glucose concentrations are low (e.g. 60 mg/dl). However, when glucose concentrations are increased (e.g. to 300 mg/dl), these agents are expected to enhance insulin secretion to levels above those seen with glucose alone (Ctl). In Figure 1, two 19AJ/RUP3 agonists, A48 and A51 enhanced glucose-dependent insulin release. Moreover, the level of enhancement was comparable to that seen with GLP-1, a gut hormone known to act on islets in this manner.

RUP3 agonists are also useful *in vivo*. In Figure 2, male C57bl/6N mice at 8 weeks of age were fasted for 18 hours and randomly grouped to receive a 19AJ/RUP3 agonist (Compound

B70) at indicated doses, or with control extendin-4 (Ex-4), a GLP-1 peptide analog known to stimulate glucose-dependent insulin secretion (Exhibit 3). Thirty minutes after administration of test compound and control Ex-4, mice were administered dextrose at 5g/kg orally. Levels of blood glucose were determined at the indicated time points using Glucometer Elite XL (Bayer). The upper panel shows the mean glucose concentration averaged from eleven animals in each treatment group. The glucose excursion curve is given in the top panel, and calculated area under curve (AUC) change in the bottom panel. Compound B70 gives a maximum reduction of AUC of 18% at a 10 mg/kg dose. These results demonstrate that the 19AJ/RUP3 agonist lowered blood glucose in a dose-dependent manner in mice after challenge with glucose.

RUP3 agonists also have utility in improving glucose homeostasis in diabetic (db) animals. As shown in Figure 3, male db mice (C57BL/KsOlahsd-Leprdb, diabetic, Harlan) at 10 weeks of age were randomly grouped to receive vehicle, Compound B70 or Ex-4 (Exhibit 4). After compound administration, food was removed and blood glucose levels were determined at the indicated times. Reduction in blood glucose at each time point was expressed as percentage of original glucose levels, averaged from six animals for each group. Treatment with Compound B70 or Ex-4 significantly reduced glucose levels compared to vehicle control. Thus, these data demonstrate that a 19AJ/RUP3 agonist, identified using the claimed invention, can improve glucose homeostasis in a diabetic animal.

Dr. Watson's Declaration also gives several other examples of orphan receptors which Applicants have correlated with a particular condition (see 22.2 (b)-(e)). These include orphan receptor 18F which is expressed in areas of the brain associated with feeding and is up-regulated in the hypothalamus of obese Zucker rats compared with lean liter mate controls (see (22.2 (b)). In addition, 18F is co-localized with AGRP, a protein known to be involved in feeding behavior. In another example, orphan receptors 19Y, 18A, and 18AI have been found to be over-expressed in particular types of tumors but not in the corresponding normal tissues (see 22.2(c)). In a further example, an orphan receptor called 19BX was found to be expressed mainly in the brain and to be abundantly expressed following cerebral artery occlusion (a model for stroke) (see 22.2 (d)). Thus, there are several examples where Applicants have correlated the location of an orphan receptor with a condition.

It is important to note that orphan receptors can have a known function even though the endogenous ligand for the receptor is not known. For example, the 19AJ /RUP3 receptor is an orphan receptor and yet it is also clearly associated with a disease (diabetes). Thus, just because an endogenous ligand is not known for a receptor, does not mean that the receptor has no utility.

Clearly, the Office Action has not established a *prima facie* showing that there is no substantial or "real world" utility. Moreover, the evidence of record shows that the claimed invention meets the standard for substantial utility and that one of ordinary skill would be able to correlate a GPCR that has a particular location in the mammal with a condition, for example, diabetes. Thus, Applicants respectfully request that the Office withdraws the rejection of claims 34, 40 and 45-70 for alleged lack of utility under 35 U.S.C. 101.

## II. The Claims Are Enabled

Claims 34, 40 and 45-70 are rejected under 35 U.S.C. 112, first paragraph, for allegedly not being enabled. Generally, the Office Action alleges that the claims are not enabled because the claimed invention does not have utility. As discussed above, Applicants respectfully assert that the claimed invention has utility. Accordingly, Applicants request that the Office withdraw any rejection under 35 U.S.C. 112, first paragraph, that is based upon an alleged lack of utility.

The Office Action also alleges that the claims are not enabled based on other grounds. Prior to addressing these other non-enablement rejections, Applicants respectfully remind the Office that it is established law that the enablement requirement of §112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of §112 requires

> nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken as in compliance with the enabling requirements of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support. (emphasis added)

Thus, any assertion by the Office that an enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974). Further, it is established law that there is no requirement at all for a "working" example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski*, 164 U.S.P.Q. 642 (C.C.P.A. 1970); *Ex parte Nardi*, 229 U.S.P.Q. 79 (Pat. Off. Bd. App. 1986). Applicants will now address the specific allegations that the claims are not enabled.

The Office Action admits that the claims are enabled for a method of screening with a constitutively activated GPCR, wherein the GPCR has been constitutively activated by (1) altering the third position removed from the beginning of the transmembrane domain represented by alignment with position 293 in the $\alpha 1\beta$-adrenergic receptor, (2) mutating the D of the DRY sequence in the second intracellular loop to any other amino acid, or (3) over-expressing. The Office Action appears to assert, however, that the claims are not enabled for any method of constitutive activation other than those recited above, apparently on the basis that methods of constitutive activation other than those disclosed in the application are not predictable for constitutively activating a novel orphan GPCR.

With respect, Applicants remind the Office that it is established law that the enablement requirement of §112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for

enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation).

Here, the claims are enabled because, without undue experimentation, a person of ordinary skill in the art, having the present specification before them, would be able to constitutively activate an orphan GPCR via both mechanisms that are taught in the application, and also by any other mechanism that was known in the art at the time for achieving such constitutive activation.

As discussed above, the Office Action admits that the specification teaches several methods for constitutively activating a GPCR that predictably produce a constitutively activated GPCR (the Office Action, page 5). It simply is not required of Applicants to list every possible method for constitutively activating a GPCR, in order to employ a step comprising such activation in a patent claim. Indeed, by proving several exemplary methods for constitutive activation, coupled with the knowledge that other methods for constitutive activation were known by those of skill in the art, Applicants clearly have met their burden for enabling the invention. Given Applicants' detailed disclosure, any assertion by the Office that those of skill in the art would be unable to use other methods of constitutive activation must be supported by evidence that such is the case, and the Office Action has clearly failed to meet this burden. Rather, the Office Action alleges that:

> Pages 38-53 of the specification discuss various means of constitutively activating different GPCRs with known ligands. All of these GPCRs and mechanisms are known in the prior art (see specification for references). These include the following mechanisms: mutational cassette (non-transmembrane or transmembrane), truncation of C-terminal tail, point mutations, anti-peptide antibodies, and overexpression. The majority of these mechanisms are specific to a particular species of GPCR. **It is not predictable that these mechanisms will work with novel orphan receptors.**

The Office Action at page 5, emphasis added. Thus, the Office Action appears to assert that the various means of constitutively activating a GPCR would not be applicable to an orphan GPCR without undue experimentation. However, this assertion is completely unsupported by any evidence whatsoever. Moreover, the assertion is factually inaccurate. As understood by one

skilled in the art, a method of constitutively activating a GPCR does not change depending on whether one knows the ligand for the GPCR. An "orphan" GPCR has the identical molecular and biochemical features of the corresponding "known" GPCR – and in fact, there is no difference whatsoever between the two, other than knowledge of an endogenous ligand for the known GPCR. For example, suppose in 1990 GPCR1 was an orphan GPCR, and then in 1991, an endogenous ligand was found for GPCR1. A method for constitutively activating the GPCR, such as over-expression that was used on the known GPCR in 1991 would work equally well on the receptor when it was an orphan GPCR in 1990. There is therefore no basis whatsoever for the Office Action's assertion that the various means of constitutively activating a GPCR would not be applicable to an orphan GPCR without undue experimentation.

In view of the detailed disclosure provided by Applicants in their specification, which thoroughly discloses various means of constitutively activating a GPCR that are well known in the art, including, for example, constitutively activating via mutational cassette (non-transmembrane or transmembrane), truncation of C-terminal tail, point mutations including those in the DRY sequence, anti-peptide antibodies, and over-expression (see the specification, for example, at pages 38-53), it is clear that those of ordinary skill in the art would be able to readily apply these various mechanisms for constitutively activating an orphan GPCR. It also is clear that the Office Action has not presented any evidence that those of skill in the art would have been unable to use other known methods in Applicants' claimed methods. Accordingly, Applicants respectfully request withdrawal of this rejection.

The Office Action also alleges that while the claims are enabled for a method of screening with an endogenous constitutively active orphan GPCR or endogenous orphan GPCR subjected to constitutive activation, wherein the orphan GPCR has been correlated with a physiological function by correlation with tissue expression, they are allegedly not enabled where the orphan GPCR has been correlated with a physiological function by any other correlation method. Applicants respectfully disagree.

One of ordinary skill would be able to employ various means of correlating an orphan GPCR with a physiological function. For example, one of ordinary skill can readily suppress the

expression of an orphan GPCR and observe the physiological changes in a mammal, thus, correlating a physiological function with the orphan GPCR. Further, one of ordinary skill would know that the suppression of the expression of an orphan GPCR may be achieved, for example, via administering an antisense oligonucleotide of the orphan GPCR to the mammal. Further, the use of antisense oligonucleotide to suppress the expression of receptors, e.g., GPCR, was well known in the art at the filing date of the present application. Also, one of ordinary skill would know that the suppression of an orphan GPCR in a mammal may be achieved, for example, via genetic knock-outs—a technology that was also well known at the filing date of the present application. For example, the specification teaches that gene targeted animals can be used to determine the physiological function of a receptor of interest (see page 66, lines 9-16). Thus, one of ordinary skill would be able to employ various means of correlating an orphan GPCR with a physiological function, other than by tissue expression. Accordingly, the claimed feature of correlating an orphan GPCR with a physiological function is fully enabled.

While the Office Action admits that the claims are enabled for a method of screening with an endogenous constitutively active orphan GPCR or endogenous orphan GPCR subjected to constitutive activation, wherein the orphan GPCR has been correlated with a physiological function by correlation with tissue expression, the Office Action nevertheless asserts that they are not enabled where the orphan GPCR has been correlated with a physiological function by any other correlation method. As an example, the Office Action cites Uhlenbrock et al., at page 8 of the Office Action and alleges that:

> evidence provided by Uhlenbrock et al. regarding the difficulty in determining the physiological function of orphan GPCRs (other than by tissue expression) is evidence that the experimentation is not routine, and therefore significant undue experimentation must be performed before the full scope of the claimed invention can be practiced.

Applicants respectfully disagree. As a preliminary matter, Applicants first note that while Uhlenbrock was apparently unable to determine a physiological role for GPR3, the present specification does shows evidence for a physiological function for GPR3 in epilepsy, for example, at page 60, lines 15-23, and Figure 15. Further, Applicants assert that one of ordinary skill in the art would be able to employ various means of correlating an orphan GPCR with a

physiological function using methods other than tissue expression, such as the methods discussed above relating to the use of antisense and knock-outs.[2] Thus, contrary to the assertion of the Office Action, those of ordinary skill in the art would have been able to employ various means of correlating an orphan GPCR with a physiological function, other than by tissue expression. Accordingly, the claimed feature of correlating an orphan GPCR with a physiological function is fully enabled.

In sum, Applicants submit that the claims are enabled for methods of constitutively activating an orphan GPCR and methods of correlating an orphan GPCR with a physiological function. Thus, Applicants respectfully request that the Office withdraws the rejection of claims 34, 40 and 45-70 for allegedly not be enabled under 35 U.S.C. 112, first paragraph.

## III. The Claims Are Fully Described

Claims 34, 40 and 45-70 are rejected under 35 U.S.C. §112, first paragraph, for allegedly not being described by the specification. Specifically, the Office Action alleges that the specification only describes three mechanisms for constitutively activating an orphan GPCR (as discussed under the enablement rejection), while the claims cover a "large number of species of methods each comprising orphan GPCRs constitutively activated by any of a variety of mechanisms". The Office Action at page 9.

The purpose of the written description requirement is to ensure that the inventor had possession of the claimed subject matter at the time the application was filed. If a person of ordinary skill in the art would have understood the inventor to possess the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the written description requirement is met. In re Alton, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996).

Applicants respectfully assert that the claims are fully described because one of ordinary

[2] The fact that there are other methods to perform such a correlation known in the art does not impose an obligation on Applicants to list them all. Indeed, it is settled law that a patent need not teach, and preferably omits, what is well known in the art. *Lindemann Maschinenfabrik v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984).

skill would have understood that Applicants possess methods for identifying a compound that stimulates an endogenous orphan GPCR or reduces the activity of an active receptor state of an endogenous orphan GPCR by constitutively activating the orphan GPCR through means other than by the three means acknowledged by the Office Action. As discussed above, various means of constitutively activating a GPCR are well known and are thoroughly disclosed by the present specification. For example, the various means of constitutively activating a GPCR disclosed by the present specification include, constitutively activating via mutational cassette (non-transmembrane or transmembrane), truncation of C-terminal tail, point mutations, anti-peptide antibodies, and overexpression. Since an orphan GPCR has all the molecular and biochemical features of a GPCR with a known ligand (see above discussion), one of ordinary skill would understand that these means of constitutively activating a GPCR would be applicable to an orphan GPCR. As such, one of ordinary skill would have understood the Applicants to possess and disclose various means of constitutively activating an orphan GPCR at the time of filing this present application. Accordingly, the claims are fully described with respect to the feature of constitutively activating an orphan GPCR by means other than the three acknowledged by the Office Action.

The Office Action further alleges that Applicants "have not provided any written description of a GPCR that has been correlated with physiological function by any means other than tissue expression." The Office Action at page 10. Again, if a person of ordinary skill in the art would have understood the inventor to possess the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the written description requirement is met. In re Alton, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996). As discussed above, various means other than by tissue expression are known for correlating an orphan GPCR with a physiological function, e.g., suppression of orphan GPCR expression in mammals and the specification specifically describes the use of transgenic and/or gene targeted animals at page 66, lines 9-16. A person of ordinary skill in the art would have understood the Applicants to possess and disclose means of correlating an orphan GPCR with a physiological function by means other than by tissue expression at the time of filing.

As was discussed above in connection with the rejection for alleged lack of enablement,

it is not incumbent upon Applicants to enable (or describe) every conceivable method for performing the steps of the claims, particularly where (as in the present case) the methods of constitutive activation and correlating a receptor with a physiologic function are known in the art. Applicants claim methods that employ orphan GPCRs that have been correlated with at least one physiological function, and Applicants' specification teaches at least two ways to perform such a correlation. A person of ordinary skill in the art would have understood the inventor to possess the various means of correlating a physiological function with an orphan GPCR at the time of filing, and the law does not require that every means of correlating be explicitly described in the specification to meet the written description requirement. In re Alton, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996).

In sum, Applicants submit that the specification sufficiently describes methods of constitutively activating an orphan GPCR and methods of correlating an orphan GPCR with a physiological function. Thus, Applicants respectfully request that the Office withdraws the rejection of claims 34, 40 and 45-70 for allegedly not being described by the specification under 35 U.S.C. 112, first paragraph.

## IV. The Claims Are Definite

Claims 34, 40, and 45-70 are rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness for "failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." The Office Action at page 11. The Office Action does not provide a basis or reason for this allegation. Accordingly, Applicants respectfully request that the Office clarify this rejection.

The Office Action alleges that claims 63, 64, 65 and 66 are indefinite for reciting a step that has no antecedent basis. Applicants have corrected typographical errors in these claims to provide antecedent basis in these claims. Thus, the amended claims are definite.

The Office Action alleges that claims 69 and 70 are indefinite because it is unclear how the inverse agonist or agonist is identified in step (b) (Applicants note that the identification step for claim 69 is step (c) ). Applicants respectfully traverse the rejection, as those of skill in the art

would readily understand how a compound that stimulates an endogenous GPCR (or an endogenous constitutively active GPCR) or reduces the activity of an active receptor state of an endogenous GPCR (or an endogenous constitutively active GPCR) can be identified. For example, the specification teaches at page 59, line 5, to page 63, line 13 the use of screening assays to identify candidate compounds as agonists or inverse agonists of GPCRs. In addition, the specification teaches several examples of screening assays including a scintillation proximity assay for cAMP, an enzyme-linked immunoassay for cAMP, measurement of cAMP by cAMP-dependent protein kinase A, and a RAS scintillation proximity assay. As such, claims 69 and 70 are definite. In addition, solely to facilitate prosecution, Applicants have amended claims 69 and 70 to clarify the identification step as based on a measurement of the ability of the compound to inhibit or stimulate functionality of the constitutively activated or constitutively active GPCR.

## V. The Claims Are Novel

Applicants respectfully traverse the rejection of claims 40, 53, 55, 56, 58, 60, 68 and 70 under 35 U.S.C. §102(e) for alleged anticipation by Gershengorn et al. (U.S. Patent No. 6,087,115).

The Office Action alleges that Gershengorn teaches methods for screening constitutively active GPCRs for test substances that negatively antagonize the activity of the receptor. In addition, the Office Action alleges that Gershengorn teaches other elements of the present claims such as GPCRs that have been correlated with a physiological function, and that non-endogenous compounds can be used in the screening method. The Office Action acknowledges that agonists are not present in the method of Gershengorn. In addition, the Office Action acknowledges that Gershengorn does determine several endogenous ligands that bind to the GPCR (see Examples section col. 8, lines 26-29); however, the Office Action alleges that "this teaching does not detract from the obviousness of using a GPCR without first identifying a ligand in the general screening method taught by Gershengorn."

Applicants respectfully note that in order for a reference to anticipate a claim, the reference must teach each and every element of the claim (MPEP 2131). The Gershengorn

reference clearly does not teach the element "wherein an endogenous ligand for said receptor has not been identified" which is an element of each of the pending claims. The Office Action acknowledges that Gershengorn does not teach a receptor "wherein an endogenous ligand for said receptor has not been identified" (an orphan receptor), but alleges that the claims are anticipated because it would be obvious that a ligand is not required for the screening method taught by Gershengorn.

Applicants respectfully submit that not requiring a ligand for receptor activation, which is the case with a constitutively active receptor, is not the same as not knowing the endogenous ligand of the receptor, which is the case with an orphan receptor. Constitutively active receptors had been known in the art at the time of the invention and it was known that such receptors can signal in the absence of a ligand. Orphan receptors were also known in the art at the time of the invention. However, it was not appreciated at the time of the invention that orphan receptors could be systematically screened by using the concept of constitutive activation. Gershengorn does not teach an orphan receptor and does not teach that orphan receptors can be screened by utilizing constitutive activation. In fact, the Gershengorn patent does not mention orphan receptors.

At the time of the invention, screening orphan receptors for modulators was attempted after first identifying a ligand for the receptor (de-orphanizing the receptor). For example, the subject specification teaches that the traditional study of receptors has always proceeded from the *a priori* assumption that the endogenous ligand must first be identified before discovery could proceed to find antagonists and other molecules which could affect the receptor (see, for example, page 29, lines 13-17). The specification further teaches that this mode of thinking has persisted in receptor research even after the discovery of constitutively activated receptors (see page 29, lines 17-20). Applicants note that this is the case with the Gershengorn patent where in the first example they identify endogenous ligands that bind to the constitutively active KSHV receptor, thus de-orphanizing the receptor (see in particular col. 8, lines 1-30).

In summary, as stated in section 2131 of the MPEP, in order to anticipate a claim a reference must teach each and every element of the claim. The Gershengorn reference does not

teach the element of the claims directed to "wherein an endogenous ligand for said receptor has not been identified." In fact, the Gershengorn reference specifically identifies endogenous ligands that bind to the KSHV GPCR. Therefore the KSHV GPCR is not an orphan receptor and Gershengorn does not teach orphan receptors. Because the Gershengorn reference does not teach each and every element of the claimed invention, the reference can not anticipate the claimed invention. Therefore, Applicants respectfully request that this ground of rejection be withdrawn.

## VI. The Claims Are Non-Obvious

Claims 34, 45, 49-51, 61 and 69 are rejected under 35 U.S.C. §103(a) for allegedly being obvious over Teitler et al. (U.S. Patent No. 6,255,089, hereinafter "Teitler") in view of O'Dowd et al. (Genomics 28:84-91, 1995, hereinafter "O'Dowd"). Applicants respectfully assert that the claims are not obvious.

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Office to provide a reason why one of ordinary skill in the art would have been led to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation **must** stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and **not** from applicants' disclosure. See for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that

> would **impel** one skilled in the art to do what the patent applicant has done.

(citations omitted; emphasis added).

Applicants note that the Teitler application 09/032,742 was filed on February 27, 1998 and claims priority to two provisional applications, the first filed on February 27, 1997 (60/039,465) and the second one filed on October 7, 1997 (60/061,268). Teitler can only be cited as prior art if the disclosure relied upon for the rejection is present in the first provisional application filed on February 27, 1997, since the filing date of the second provisional application and filing date of the regular application are after the priority date of the subject application (April 14, 1997). Applicants have obtained a copy of provisional application 60/039,465, filed on February 27, 1997 and have attached the specification of this application herewith as Exhibit 5 for the Examiner's convenience.

Significantly, the Office Action identifies no "motivating force" that would "impel" persons of ordinary skill to modify Teitler in view of O'Dowd to achieve the claimed method, *wherein an endogenous ligand for said receptor has not been identified.* The Office Action provides as motivation to modify Teitler in view of O'Dowd that Teitler teaches

> [t]he importance of constitutively activated receptors to biological research cannot be overstated...the existence of constitutively activated receptors provides a novel screening mechanism with which compounds which act to increase or decrease receptor activity can be identified and evaluated. Such compounds may become lead compounds for drug research.

The Office Action at page 17. This quote is derived from Teitler application 09/032,742 filed on February 27, 1998; however, this teaching does **not** appear in provisional application 60/039,465, filed February 27, 1997. Indeed, provisional application 60/039,465 does not teach several of the items which appear in the later filed U.S. regular application. Accordingly, provisional application 60/039,465 does not provide any teaching or suggestion that would motivate one to combine its disclosure with that of O'Dowd.

Further, Applicants submit that Teitler's description of constitutive active receptors in provisional application 60/039,465 does not teach or suggest that orphan receptors can be

systematically screened using constitutive activation and there is no teaching or suggestion in Teitler to impel one skilled in the art to do what the subject application has disclosed. Teitler does not teach or suggest the claimed methods which recite *wherein an endogenous ligand for said receptor has not been identified.*

O'Dowd does not cure the deficiency of Teitler. That is, one of ordinary skill in the art would not be impelled by the teaching of O'Dowd to modify the teaching of Teitler to arrive at the present invention. O'Dowd teaches an orphan GPCR, GPR8, that is located specifically in the frontal cortex in humans. However, O'Dowd does not teach or suggest the use of constitutively active orphan GPCR for identifying a non-endogenous candidate compound as a compound that stimulates an endogenous GPCR (or an endogenous constitutively active GPCR) or reduces the activity of an active receptor state of an endogenous GPCR (or an endogenous constitutively active GPCR).

Therefore there is no motivation to combine the Teitler reference which can properly be used as prior art (60/039,465) and O'Dowd. As such, the claims are not obvious over Teitler in view of O'Dowd. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. §103(a).

Claims 52, 62, 67 and 69 are rejected under 35 U.S.C. §103(a) for alleged obviousness over Teitler in view of Scheer et al (Proc Natl Acad Sci USA 94:808-813 (1997), hereinafter "Scheer") and in further view of Xu et al (Genomics 35:397-402 (1996), hereinafter "Xu"). As discussed above, Teitler does not teach or suggest the claimed method, *wherein an endogenous ligand for said receptor has not been identified.* Scheer discloses constitutive activation of a known receptor by mutation of a D residue in the DRY sequence, and Xu discloses an orphan receptor with a DRY sequence. Similar to O'Dowd, neither of these references would impel one of ordinary skill to modify Teitler to achieve the claimed method, *wherein an endogenous ligand for said receptor has not been identified.* Applicants therefore respectfully request withdrawal of this rejection under 35 U.S.C. §103(a).

Applicants respectfully submit that this application is in condition for allowance, and respectfully request early notification of the same. Applicants invite the Examiner to contact the undersigned at (215) 665-2158 to clarify any unresolved issues raised by this amendment.

Respectfully submitted,

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